The Protective Effect of Middle Cerebral Artery Calcification on Symptomatic Middle Cerebral Artery Infarction

Jang-Hyun Baek, MD; Joonsang Yoo, MD; Dongbeom Song, MD; Young Dae Kim, MD, PhD; Hyo Suk Nam, MD, PhD; Ji Hoe Heo, MD, PhD

***Background and Purpose*—**The presence of intracranial artery calcification is associated with an increased risk for stroke. However, calcified atherosclerotic plaques are also known to be less vulnerable to rupture. Given this discrepancy, we investigated whether the vulnerability of intracranial arterial atherosclerosis differed based on the presence or absence of calcification.

Methods—We considered consecutive patients with acute stroke in the unilateral middle cerebral artery (MCA) territory. Patients with any stenotic MCAs were included in this study. Symptomatic MCA was defined as the occurrence of infarctions relevant to the stenotic MCA. The presence of calcification in the MCA was evaluated on noncontrast thin-section computed tomography images using a 3dimensional software package. Generalized estimating equations were used to compare the frequency of calcification between symptomatic and asymptomatic stenosis.

Results—Of the 1066 MCAs examined in 533 patients, 645 MCAs were stenotic and were included in the study. Among the 645 stenotic MCAs, 406 MCAs (62.9%) were symptomatic. Calcification was observed in 36 MCAs (5.6%). Calcification in the MCA was more frequently observed in the asymptomatic group (7.9% versus 4.2%; P=0.032). On multivariable analysis, the presence of calcification in MCA atherosclerosis was less frequent in the symptomatic group (odds ratio, 0.46; 95% confidence interval, 0.23–0.92; P=0.027).

Conclusions—This study showed that calcified atherosclerosis in the MCA was less frequently symptomatic. **(*Stroke*. 2017;48:3138-3141. DOI: 10.1161/STROKEAHA.117.017821.)**

Key Words: atherosclerosis ■ intracranial stenosis ■ stroke ■ vascular calcification

Plaque calcification is considered an active process of atherosclerosis and is, thus, often used as an indirect marker for atherosclerosis.[1] According to epidemiological studies, intracranial artery calcification (IAC) is a risk factor for stroke.[2] The burden of IAC is related to the development, progression, and recurrence of stroke. In contrast, the presence of calcification in the atherosclerotic vessels correlates with stable, noninflammatory, and asymptomatic plaques.[3,4] Given the discrepancies, questions have arisen as to whether IAC actually increases the risk of stroke or is merely a bystander of advanced, coexisting atherosclerosis.

Most previous studies on IAC have been undertaken without consideration of arterial stenosis at the site of IAC.[2] Thus, the clinical role of IAC in atherosclerotic stenosis has not been well understood.[5] In addition, the frequency of arterial calcification is different between the carotid artery and distal intracranial arteries, such as the anterior, middle, and posterior cerebral arteries.[6]

To investigate the effect of IAC on atherosclerotic vulnerability, we compared the frequency of arterial calcification between symptomatic and asymptomatic stenosis of the middle cerebral artery (MCA).

Methods

Study Population

This was a retrospective, cross-sectional study that considered consecutive patients with acute cerebral infarction within 7 days of symptom onset who were admitted from January 2005 to December 2014 and enrolled in the prospective stroke registry. Of these patients, we considered patients with a cerebral infarction in the unilateral MCA territory for this study. Patients with coexisting infarctions in arterial territories other than the MCA were excluded. We also excluded patients with high-risk sources of cardioembolism, other obvious etiologies such as arterial dissection, or complete occlusion of the MCA with a pathogenesis that could not clearly be determined. Then, we selected patients who had MCA stenosis, either in the symptomatic side (ipsilateral to the MCA infarction) or in the asymptomatic side (contralateral to the MCA infarction).

Stroke Evaluation

Patients were routinely evaluated using a thin-section noncontrast computed tomography (CT) scan at admission, magnetic resonance

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From the Department of Neurology, Yonsei University College of Medicine (J.-H.B., J.Y., D.S., Y.D.K., H.S.N., J.H.H.) and Department of Neurology, National Medical Center (J.-H.B.), Seoul, Republic of Korea.

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Correspondence to Ji Hoe Heo, MD, PhD, Department of Neurology, Yonsei University College of Medicine, 50–1 Yonsei-ro, Seodaemoon-gu, 03722, Seoul, Republic of Korea. E-mail jhheo@yuhs.ac

imaging, including diffusion-weighted imaging, within 2 days of admission, and cerebral angiographic studies (at least one each of a digital subtraction angiography, CT angiography, and magnetic resonance angiography). Standard cardiac evaluations included 12-lead electrocardiography, echocardiography, heart CT, and continuous electrocardiography monitoring in the stroke unit or Holter monitoring. During the regular stroke conference, the territory of infarctions was determined based on consensus of stroke neurologists. The presence and the degree of arterial stenosis were also measured, and these data were then entered into the prospective registry. For this study, arterial stenosis was categorized into normal (0%), mild (<50%), moderate (50% to 75%), and severe (>75%).

Imaging and Data Analysis

MCA calcification was qualitatively evaluated on 1.00 or 1.25 mm thin-section noncontrast CT images using a 3-dimensional software (Xelis; Infinitt, Seoul, Korea).[7] After adjustment of the window level (500 Hounsfield units [HU]) and the window width (2500 HU), pixels within the region of interest at the MCA that were above the predefined 130 HU threshold were automatically highlighted.[8] For all defined cases, CT or magnetic resonance angiography source images were reassessed to confirm that the calcification was in fact located on the MCA.

The stenotic MCA was regarded as symptomatic when there was an infarction in the ipsilateral MCA territory. We compared the frequency of calcified MCAs between the symptomatic and asymptomatic MCA groups. To calculate the correlation of bilateral MCAs selected from the same patient, generalized estimating equations were used to compare demographic and imaging findings. Multivariable analysis was also performed by entering all variables into the generalized estimating equations. This study was approved by the Institutional Review Board of Yonsei University Health System.

Results

A total of 590 patients were included based on inclusion and exclusion criteria (Figure). Among these patients, 533 were evaluated because 57 did not undergo noncontrast thin-section CT scans. Mean age of the 533 patients was 66.8±12.3 years, and 290 patients (54.4%) were men. Of the 1066 MCAs assessed in the 533 patients, 645 were stenotic MCAs (406 symptomatic [62.9%] and 239 asymptomatic [37.1%]).

The symptomatic MCA group was younger and more frequently had hypertension, diabetes mellitus, or hypercholesterolemia, compared with the asymptomatic MCA group (Table). MCA stenosis was more severe in the symptomatic MCA group. MCA calcification was observed in 36 (5.6%) of all stenotic MCAs. Severe stenosis tended to be more common in calcified MCAs than in noncalcified MCAs (16.7% versus 9.5%; P=0.075; Table I in the online-only Data Supplement). MCA calcification was more frequent in the asymptomatic MCA group (7.9% versus 4.2%; P=0.032). On multivariable analysis, the MCA calcification was independently associated with asymptomatic MCA stenosis (odds ratio, 0.46; 95% confidence interval, 0.23–0.92). These associations between MCA calcification and asymptomatic MCA stenosis were also demonstrated in the subgroup analysis in patients with first-ever unilateral MCA infarction (Table II in the online-only Data Supplement).

Discussion

This study showed that calcification was infrequent among stenotic MCAs but was more frequently found with asymptomatic MCA stenosis than with symptomatic MCA stenosis. This finding suggests that noncalcified plaques are more vulnerable than calcified plaques. Active inflammatory conditions make plaques more vulnerable. Compared with calcified plaques, noncalcified plaques showed more macrophage infiltration and

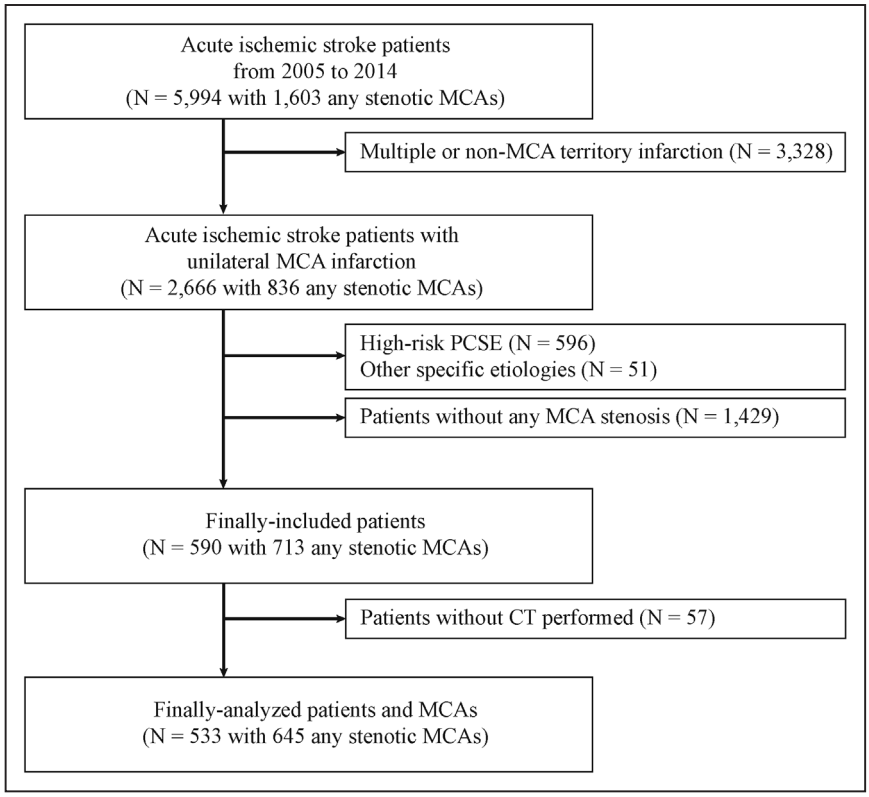

Figure. Patient selection flowchart. CT indicates computed tomography; MCA, middle cerebral artery; and PCSE, potential cardiac source of embolis.

Table. Comparison of Patient Demographics and Arterial Findings Between Asymptomatic and Symptomatic Middle Cerebral Artery

	Univariable Analysis			Multivariable Analysis	
	Asymptomatic MCA (n=239)	Symptomatic MCA (n=406)	*P* Value	Odds Ratio (95% CI)	*P* Value
Patient demographics					
Age, y	70.0±10.9	65.7±12.5	0.001	0.97 (0.96–0.98)	0.001
Sex, men	123 (51.5)	225 (55.4)	0.228	1.07 (0.77–1.48)	0.687
Hypertension	181 (75.7)	340 (83.7)	0.005	1.90 (1.31–2.75)	0.001
Diabetes mellitus	86 (36.0)	174 (42.9)	0.033	1.22 (0.92–1.63)	0.170
Hypercholesterolemia	36 (15.1)	83 (20.4)	0.039	1.09 (0.73–1.61)	0.684
Current smoking	58 (24.3)	110 (27.1)	0.329	0.91 (0.63–1.32)	0.630
Arterial findings					
Associated ICA stenosis			0.302		
No stenosis	141 (59.0)	267 (65.8)		Reference	
Mild	72 (30.1)	105 (25.9)		0.86 (0.60–1.22)	0.392
Moderate	21 (8.8)	27 (6.7)		0.78 (0.41–2.59)	0.442
Severe	5 (2.1)	7 (1.7)		0.92 (0.28–3.06)	0.891
MCA stenosis			0.001		
Mild	175 (73.2)	208 (51.2)		Reference	
Moderate	55 (23.0)	143 (35.2)		2.16 (1.49–3.13)	0.001
Severe	9 (3.8)	55 (13.5)		5.03 (2.39–10.6)	0.001
Calcified MCA	19 (7.9)	17 (4.2)	0.032	0.46 (0.23–0.92)	0.027

Values are mean±standard deviation, number (%), or odds ratio (95% confidence interval). CI indicates confidence interval; ICA, internal carotid artery; and MCA, middle cerebral artery.

a higher expression of inflammatory markers, including monocyte chemoattractant protein-1 and interleukin-8.[3,4] Products related to osteogenesis, such as interleukin-1, bone morphogenetic protein-6, and osteocalcin, were detected in the fibrous cap of plaques and were negatively associated with inflammation.[4] In addition, a computational model revealed that calcification in the fibrous cap could also result in physical stability, which would protect against rupture.[9] Our findings suggest that IAC might offer protective effects on plaque vulnerability, as does plaque calcification in the extracranial carotid artery.[3–5]

The presence and burden of IAC were associated with an increased risk for stroke.[2] However, in previous studies, IAC was merely considered to be a marker for advanced coexisting atherosclerosis.[2] In this study, calcified MCA stenosis tended to be more frequently associated with severe stenosis but was less frequently symptomatic, which supports previous findings.[3,4,9]

This study has limitations. First, it does not show a direct causal relationship between IAC and cerebral infarction because of its cross-sectional design. Furthermore, symptomatic was defined as an acute infarction within 7 days of onset. Although some patients might have old infarctions, they were not regarded as symptomatic because the exact temporal relationship between old infarctions and MCA stenosis was uncertain. However, the significance of calcified MCA on symptomatic MCA infarction was not changed in the subgroup analysis of patients with first-ever stroke. Second, this study included only cases of MCA stenosis. Therefore, it is uncertain whether our findings are also applicable to IAC in other intracranial arteries, including the internal carotid artery, in which IAC is common.

Conclusions

Calcification in atherosclerotic lesions of the MCA was infrequent. However, the presence of IAC was less frequently associated with symptomatic lesions. Our findings support previous studies in coronary or extracranial carotid artery disease that the calcified plaque is less vulnerable to rupture.

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Disclosures

None.

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